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# TRANSMITTAL FORM

*(to be used for all correspondence after initial filing)*

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|---|---|
| Total Number of Pages in This Submission | 1 |

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| Application Number | 10/626,301 |
| Filing Date | July 23, 2003 |
| First Named Inventor | Hutchens, T. William |
| Art Unit | 1639 |
| Examiner Name | Teresa D. Wessendorf |
| Attorney Docket Number | 016866-002220 |

## ENCLOSURES *(Check all that apply)*

- ☐ Fee Transmittal Form
  - ☐ Fee Attached
- ☐ Amendment/Reply
  - ☐ After Final
  - ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Reply to Missing Parts/ Incomplete Application
  - ☐ Reply to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
  - ☐ Landscape Table on CD
- ☐ After Allowance Communication to TC
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☒ Other Enclosure(s) (please identify below):
  - Communication
  - Declaration of Lee O. Lomas Under 37 CFR 1.132 w/Exhibits A-B
  - Return Postcard

**Remarks** The Commissioner is authorized to charge any additional fees to Deposit Account 20-1430.

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

| | | | |
|---|---|---|---|
| Firm Name | Townsend and Townsend and Crew LLP | | |
| Signature | Eugenia Garrett-Wackowski | | |
| Printed name | Eugenia Garrett-Wackowski | | |
| Date | | Reg. No. | 37,330 |

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

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|---|---|---|---|
| Signature | Linda Shaffer | | |
| Typed or printed name | Linda Shaffer | Date | 10/28/05 |

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| In re application of: | Confirmation No. 1861 |
| T. William Hutchens *et al.* | Examiner: Teresa D. Wessendorf |
| Application No.: 10/626,301 | Technology Center/Art Unit: 1639 |
| Filed: July 23, 2003 | |
| For: RETENTATE CHROMATOG RAPHY AND PROTEIN CHIP ARRAYS WITH APPLICATIONS IN BIOLOGY AND MEDICINE | COMMUNICATION FORWARDING DECLARATION OF LEE O. LOMAS, PH.D. UNDER 37 CFR § 1.132 |
| Customer No.: 53671 | |

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Amendment and related documents filed on September 19, 2005 in response to the Office Action mailed May 19, 2005, enclosed is the executed Declaration of Lee O. Lomas, Ph.D. under 37 C.F.R. § 1.132.

It is pointed out that the Amendment indicated that an executed Declaration of Tai-Tung Yip under 37 C.F.R. § 1.132 would be forthcoming. However, upon further discussions with Drs. Yip and Lomas, it was determined that since Dr. Lomas was the scientist that personally carried out the work that is the subject of the declaration, it would be more appropriate for the declaration to come from Dr. Lomas. As such, Applicants provide the Examiner with the executed Declaration of Lee O. Lomas, Ph.D. under 37 C.F.R. § 1.132.

As set forth in the Amendment, the § 1.132 Declaration of Lee O. Lomas, Ph.D. is provided to confirm the operability of the presently claimed methods. As attested to by Dr. Lomas in his declaration, the methods of the present invention can be predictably and successfully carried out without undue experimentation. In fact, the example provided with Dr. Lomas' declaration demonstrates translation in an *E. coli* cell. As the Examiner is aware, the

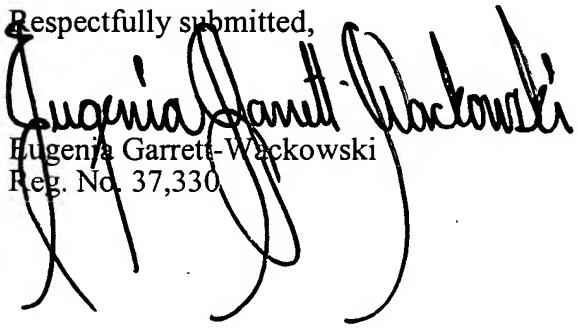
presently claimed methods set forth carrying out *in vitro* translation. However, it is the opinion of Dr. Lomas that mRNA can be provided via an expression system or in an already transcribed form (*e.g.*, via a commercially purchased mRNA library). In fact, according to Dr. Lomas, commercially purchased reagents for carrying out *in vitro* translation can be added to the well created by the cylindrical tube, and the translated polypeptide can be captured using an appropriate adsorbent. As such, it is the opinion of Dr. Lomas that the specification, as filed, teaches those of skill in the art how to practice the present methods without undue experimentation.

## CONCLUSION

In view of the previously filed Amendment and the executed Declaration of Lee O. Lomas, Ph.D., Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Eugenia Garrett-Wackowski
Reg. No. 37,330

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 925-472-5000
Fax: 415-576-0300
Attachment
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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|
| In re application of: | Confirmation No. 1861 |
| T. William Hutchens *et al.* | Examiner: Teresa D. Wessendorf |
| Application No.: 10/626,301 | Technology Center/Art Unit: 1639 |
| Filed: July 23, 2003 | DECLARATION OF LEE O. LOMAS UNDER 37 C.F.R. § 1.132 |
| For: RETENTATE CHROMATOGRAPHY AND PROTEIN CHIP ARRAYS WITH APPLICATIONS IN BIOLOGY AND MEDICINE | |
| Customer No.: 53671 | |

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Lee O. Lomas, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both, under 18 U.S.C. § 1001, and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I am currently a Director of Biology Research and Development Ciphergen Biosystems, Inc., Fremont California. Prior to that, I have held the following positions:

Manager of Biology Research, Ciphergen Biosystems, Fremont, CA, USA.
European Senior Research Scientist, Ciphergen Biosystems, Surrey, UK
Field Research Scientist, Ciphergen Biosystems, Surrey, UK
Research Associate, University of Liverpool, Liverpool, UK.

3. I hold a Ph.D. from the Department of Zoology at the University of Alberta in Edmonton, Alberta, Canada. I earned a B. Sc. from the Department of Biological Sciences at the University of Alberta.

4. My current research interests include applying SELDI mass spectrometry technologies to the understanding of biological systems. I am an inventor on numerous patent applications in this area as well as an author or co-author on many publications and presentations. My *Curriculum Vitae* is attached as Exhibit A.

6. I have reviewed the specification and the presently pending claims for the above-referenced application.

7. The presently claimed methods for detecting translation of an mRNA can be carried out methodically and predictably without undue experimentation.

8. Attached to this Declaration as Exhibit B is an example of an experiment executed by myself, wherein a protein translated in a cylindrical well attached to a mass spectrometry substrate was methodically and predictably bound to an adsorbent and then detected by mass spectrometry.

9. The example attached to this Declaration teaches all of the steps of the claimed methods for the present application:

a) providing a substrate for use in desorption spectrometry, wherein the substrate comprises a surface and an adsorbent attached to the surface;

b) providing an mRNA encoding a polypeptide and reagents for translation of the mRNA;

c) translating the mRNA *in situ* on the substrate, whereby the polypeptide is produced and is bound through the adsorbent to the substrate;

d) exposing the substrate to an eluant to wash off unbound material and to allow retention of the polypeptide by the adsorbent; and

e) detecting retained polypeptide by desorption spectrometry.

10. The example attached to this Declaration differs from the pending claims of the present application in that in the example, the protein is translated in an *E. coli* cell, and in the claims, the protein is translated *in vitro*. However, protocols for *in vitro* translation were well known and commonly practiced at the time of the June 20, 1997 priority date of the present application. Kits were readily purchasable from, for example, Promega of Madison, Wisconsin at that time.

11. In view of the teachings provided in the specification and the Example attached as Exhibit B, it is my opinion that the presently claimed methods for detecting translation of an mRNA can be carried out methodically and predictably without undue experimentation.

The declarant has nothing further to say.

Lee O. Lomas

Lee O. Lomas

Oct 12, 05.

Date

# Lee O Lomas, PhD

2848 El Capitan Drive, Pleasanton, CA, 94566.
Telephone: 510-505-2243 (W); 925-218-4577 (H); cell: 510-673-9718; Fax 510-505 –2101
e-mail: lomas@ciphergen.com

DOB: 01/30/1964
Citizenship: Canadian

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**Education:**

1993 Ph.D. Department of Zoology, University of Alberta, Edmonton, Alberta, Canada.

1988 B. Sc. (Specialization), Department of Biological Sciences, University of Alberta, Edmonton, Alberta, Canada.

**Research and Commercial Experience Overview:**

2004-Present **Director Biology Research and Development**, Ciphergen Biosystems Inc., Fremont, CA. USA.

- Oversee applications and chemistry research and development programs directed to the life science market. This includes new applications and application specific components, both reagents and new array chemistries that enable current and future customers.
- Evaluate emerging technologies for competitive and/or synergistic relationships and develop collaborative relationships where mutual benefit exists.
- Invent new technologies/methodologies to provide innovative solutions to unmet customer needs.
- Interact directly with Marketing and Manufacturing groups to define product specifications and ensure effective transfer into production.
- Represent Ciphergen's technology in both high-level business situations as well as conferences.

2001 – 2003 **Manager, Biology Research**, Ciphergen Biosystems Inc, Fremont, California, USA.

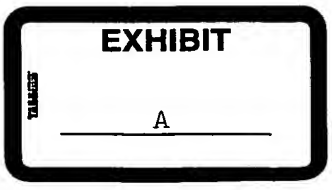
- Oversee day-to-day operations of a group of 9 scientists given the task of developing new surface chemistries and applications to drive the ProteinChip technology forward in the market place.
- Report directly to senior management on progress of each project
- Provide technical support for Marketing and Manufacturing.
- Work directly with the Sales team to support instrumentation placement through targeted application demonstration.

2000-2001 **European Senior Research Scientist**, Ciphergen Biosystems Ltd., The Surrey Research Park, Guildford, Surrey, UK..

- Provided high-level technical demonstrations of Ciphergen's ProteinChip technology to key pharmaceutical and academic accounts.
- Provided advanced technical training to Ciphergen's customer base in the areas of protein identification and protein-protein interactions.
- Trained junior applications scientists and oversaw European technology demonstrations.
- Produced application-focused literature for internal and local marketing purposes.
- Represent Ciphergen at internationally attended conferences and trade shows.

1998-2000 **Field Research Scientist**, Ciphergen Biosystems Ltd., The Surrey Research Park, Guildford, Surrey, UK.

- Applications specialist within the UK and provide sales support to our UK country manager.
- Contacted perspective customers, prepared detailed technical presentations and carrying out on-site instrument demonstrations.
- Provided initial instrument installation, customer training, specific applications development and all aspects of instrumentation service and repair.



1994-1998 **Research Associate**, Department of Biochemistry, University of Liverpool, Liverpool, U.K. Project title: "Developmental hormones in selected invertebrates". Funded by The Wellcome Trust, Grant No. 043565/Z/95/Z/JRS/SH and Grant No. 039578/A/93/Z/JRS/MW/cg.

- Discovered and demonstrated that a neuropeptide (later named ecdysiotropic neurohormone; EtNH) is responsible for stimulating the production of ecdysteroid hormones from epidermal tissues in ticks. This is the first, and to date, and only identification of such a neuropeptide-ecdysteroid hormonal axis in ticks.
- Began the purification, characterization, and initial molecular cloning of EtNH. EtNH was purified to homogeneity and internal amino acid sequence information was obtained.
- Described the first series of signal transduction pathways leading to the action of EtNH.
- Technical experience included sterol purification, radiolabelled tracer studies, GC- and APCI-MS (steroid chemistry) and metabolic labeling, purification and purity assessment, second messenger system studies, ES- and nano-ES-mass spectrometry (protein chemistry).
- Other responsibilities included supervision of PhD students and technicians in the laboratory, actively involved in devising suitable honors research projects for undergraduate students relating to aspects of tick biochemistry, and preparation, and manning of laboratory displays used for University open-day events.

## Publications:


**Lomas, L.O.** 2004. Use of ProteinChip Arrays for Deciphering Biological Pathways. In Protein Microarray Technology, ed Dev Kambhampati, pp. 153-164.

**Lomas, L.O.** 2002. Applications of ProteinChip® Systems in Toxicological Assessment. .Springer-Verlag Tokyo Berlin Heidelberg New York London Paris Hong Kong,.

**Lomas, L.O.**, Gelman, D. and Kaufman, W.R. Ecdysteroid regulation of salivary gland degeneration in the ixodid tick, *Amblyomma hebraeum*: A reconciliation of *in vivo* and *in vitro* observations. General and Comparative Endocrinology, Vol. 109, 200-211.

**Lomas, L.O.** and Rees, H.H. 1998. Endocrine regulation of development and reproduction in acarines. In Arthropod Endocrinology: Perspectives and Recent Advances', G.M. Coast and S.G. Webster (eds.), Cambridge University Press, Cambridge, pp. 91-124.

**Lomas, L.O.**, Turner, P.C. and Rees, H.H. 1997. A novel neuropeptide-endocrine interaction controlling production in ixodid ticks. Proceedings Of The Royal Society Of London Series B-Biological, Vol. 264, pp. 589-596.

**Lomas, L.O.**, Black, J.C. and Rees, H.H. 1996. Evidence for the existence of juvenile hormones in ticks. Biochemical Society Transactions, Vol. 24, p. S437.

**Lomas, L.O.** and Kaufman, W.R. 1992. Influence of a male derived protein factor on salivary gland degeneration in the female tick Amblyomma hebraeum. First International Conference on Tick-Borne Pathogens at the Host-Vector Interface: An Agenda for Research. University of Minnesota, USA, pp. 165-170.

**Lomas, L.O.** and Kaufman, W.R. 1992. The influence of a factor from the male genital tract on salivary gland degeneration in the female ixodid tick, *Amblyomma hebraeum*. Journal of Insect Physiology, Vol. 38, pp. 595-601.

**Lomas, L.O.** and Kaufman, W.R. 1992. An indirect mechanism by which a protein from the male gonad hastens salivary gland degeneration in the female ixodid tick, *Amblyomma hebraeum*. Archives of Insect Biochemistry And Physiology, Vol. 21, pp. 169-178.

**Lomas, L.O.** and Kaufman, W.R. 1991. Ivermectin is not an agonist at a γ-receptor in tick salivary glands. Experimental & Applied Acarology, Vol. 12, pp. 129-133.

Annalisa Castagna, Daniela Cecconi, Lau Sennels, Juri Rappsilber, Luc Guerrier,
Frederic Fortis, Egisto Boschetti, **Lee Lomas**, and Pier Giorgio Righetti. Exploring the Hidden Human Urinary Proteome via Ligand Library Beads. J of Proteome Research, In Press

Pier Giorgio Righetti, Annalisa Castagna, Francesca Antonucci, Chiara Piubelli, Daniela Cecconi, Natascia Campostrini, Chiar Rustichelli, Paolo Antonioli, Gianluigi Zanusso, Salvatore Monaco, **Lee Lomas,** Egisto Boschetti. Proteome analysis in the clinical chemistry laboratory: Myth or reality? Clinica Chimica Acta 357 (2005) 123–139.

Thulasiraman V, Lin S, Gheorghiu L, Lathrop J, **Lomas L,** Hammond D, Boschetti E. 2005. Reduction of the concentration difference of proteins in biological liquids using a library of combinatorial ligands. Electrophoresis, Vol 26, 3561-3571.

Fung E.T., Yip T.T., **Lomas L.O.**, Wang Z., Yip C., Meng X-Y., Lin S., Zhang F., Zhang, Z., Chan D.W., Weinberger S.R.. 2005. Classification of cancer types by measuring variants of host response proteins using SELDI serum assays. J Cancer Jul 10;115(5):783-9.

Guerrier G, **Lomas L**, Boschetti E. 2005. Multifunctional fractionation of proteomes combined with surface enhanced laser desorption ionization mass spectrometry analysis. J. Chromatography A. in press.

Zheng Wang, Christine Yip, Yong Ying, Jing Wang, **Lee Lomas,** Tai-Tung Yip, Eric T. Fung. Development of a serum assays for the diagnosis of early stage ovarian cancer using SELDI-TOF-MS. Clinical Chem. 50:1939-42 (2004).

Ren Lai, Hajime Takeuchi, **Lee O. Lomas**, Jan Jonczy, Daniel J. Rigden, Huw H. Rees, and Philip C. Turner. A new type of antimicrobial protein with multiple histidines from the hard tick, *Amblyomma hebraeum*. The FASEB Journal Published online July 9, 2004.

Lai, R; **Lomas, L;** Jonczy, J; Turner, PC; and Rees, HH. Two novel non-cationic defensin-like antimicrobial peptides from haemolymph of the female tick, *Amblyomma hebraeum*. 2004. Biochemical Journal.
Kaufman, W.R. and **Lomas, L.O.** 1996. Male factors in ticks: Their role in feeding and egg development. Invertebrate Reproduction & Development, Vol. 30, pp. 191-198.

Thulasiraman, V; Wang, Z; Katrekar A; **Lomas, L** and Yip, TT. 2004. Simultaneous Monitoring of Multiple Kinases Activities by SELDI-Mass Spectrometry. In Methods in Molecular Biology, ed Eric Fung,

Wainwright, G., Prescott, M.C., **Lomas, L.O.**, Webster, S.G. and Rees, H.H. 1997. Development of a new high-performance liquid chromatography spectrometric method for the analysis of ecdysteroids in biological extracts. Archives Of Insect Biochemistry And Physiology, Vol. 35, pp. 21-31.

Wainwright, G, Prescott, M.C., **Lomas, L.O.**, Webster, S.G. and Rees, H.H. 1996. Trace analysis of arthropod hormones by liquid-chromatography atmospheric-pressure chemical-ionization mass-spectrometry. Biochemical Society Transactions, Vol. 24, p. S476.

## Patents and Patent Applications:

- **Lomas, L.O**. Biomolecule characterization using mass spectrometry and affinity tagging. US2003/PCT 0077616A1.
- Boschetti E, Bradbury L, Davies H, **Lomas LO**, Pham T, Thulasiraman, V and Yip TT. Methods for monitoring polypeptide production and purification using surface enhanced laser desorption/ionization mass spectrometry. US2003/PCT 0091976A1.
- **Lomas LO**, Thulasiraman V and Yip TT. Detection of kinase substrates and products using ion mass spectrometry. US2004/PCT0029191A1.
- Rich W E, Boschetti E, **Lomas LO** and Yip TT. Protein interaction difference mapping. US2004/ PCT0146937.
- Pac B, Fu, S, **Lomas LO**, Tornatore P, Viner R, Weinberger SR, Yip TT, Tyler S, Jones S, Bastien N, Plummer F, Feldmann H and LI Y. Sars virus polypeptides. WO2004/PCT092332A2.
- Boschetti E and **Lomas LO**. Allergen test devices and methods for their use. WO2004/PCT104586A1.
- Ding J and **Lomas LO**. Serum biomarkers in Ischaemic heart disease. WO2004/PCT 111654A2.

## EXHIBIT B

**EXAMPLE 1: On-chip Monitoring of recombinant His-PelleC protein expression in *E. coli* by SELDI**

**Cell culture and expression system**

IPTG inducible vector pQE30 (Qiagen) was used to clone the His-PelleC gene. The protein was expressed in *E. coli*. M15 cells. An overnight culture of *E. coli* cells containing the expression plasmid of interest was grown up in 5 ml of LB/antibiotics at 37°C. The culture was diluted 1:10 in fresh LB/antibiotics before loading onto chips.

**Preparation of IMAC-3-Ni chips and on-chip growth**

IMAC-3 chips were charged with 5 µl of 50mM nickel chloride for 5 min each, twice, followed by rinsing with 5 µl of water once and 5 µl of PBS twice for 5 min each. Load the chips in a 96-well format bio-processor. In each well, aliquot diluted cell culture in a volume varying from 10 µl to 125 µl. The cells were grown for 1.5 hrs at 37°C until $OD_{600}$ reaches 0.6. IPTG was added to a final concentration between 0 to 1 mM. The cells were grown for an additional 1-3 hrs at 37°C to allow protein expression. A schematic diagram is outlined in Figure 1.

**Lysis of cells and binding of His-tagged protein to IMAC-Ni surface**

At the end of induction, the cells were spun down in the bio-processor at 2,000 rpm for 10 min at 4°C and medium was removed from each well. Ten micro liters of a buffer containing 50 mM $NaH_2PO_4$, 300 mM NaCl, 10 mM imidazole and 1 mg/ml lysozyme, pH 8 was added to each well. The cells were lysed for 30 min before 90 µl of the buffer (50 mM $NaH_2PO_4$, 300 mM NaCl, 10 mM imidazole) was added to dilute out the lysozyme. Continue incubation for 1 hr to allow binding of His-tagged protein to the surface (Figure 6).

Alternatively, at the end of induction, the cells were not centrifuged, instead a 10x solution containing 10 mg/ml lysozyme was added directly to the medium in the wells to lyse the cells for 30 min. Continue to incubate in the same medium for 1 hr.

At the end of 1 hr, the solution was removed, and 100 μl of a buffer containing 50 mM $NaH_2PO_4$, 300 mM NaCl, 20 mM imidazole and 0.05% Tween-20, pH 8 was added to each well to wash for 5 min, 3 times. The chips were then rinsed with water and allowed to dry. Energy-absorbing matrix (EAM) was added to spots. The chips were ready for MS analysis. Broth volume optimization is shown in Figure 3 while a comparison of the two methods of *E. coli* disruption are shown in Figure 4.